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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

RUSSEL, JEFFREY E

ART UNIT PAPER NUMBER

1654

DATE MAILED: 06/12/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/815,978

Applicant(s)

SCHWARTZ, DAVID A.

Examiner

Jeffrey E. Russel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 54-70 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 54, 55 and 57-70 is/are rejected.
- 7) ☒ Claim(s) 56 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 April 2001 and 30 April 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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1. Applicant's election of the species defined by structure in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It should be noted, contrary to Applicant's Introductory Comments at page 1 of the response filed April 30, 2003, that claim 3 was not withdrawn by the examiner from consideration in the previous Office action. Rather, claim 3 was held to be an elected claim, and was indicated to be novel and unobvious over the prior art of record (see paragraph 18 of the Office action mailed January 9, 2003).

2. The Sequence Listing filed April 30, 2003 is approved.

3. Claims 54, 55, and 57-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 54 is indefinite because it recites what appears to be an alternative definition "or (ii)" (see page 3, line 2, of Applicant's response filed April 30, 2003), but the first alternative definition "(i)" is not present in the claim. Claim 63 is unclear because it recites that the surface has an amino reactive moiety. However, because the independent claim 54 defines B as being an amino reactive moiety, it is not clear how the amino reactive moiety of the compound of formula I could react with the amino reactive moiety of the surface in claim 63. It is possible that Applicant intended to recite that the surface of claim 63 has an amino moiety, with which the amino reactive moiety of the compound can react. Claim 70 is indefinite because it is dependent upon canceled claim 1.

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4. Claims 54, 55, and 57-70 are objected to because of the following informalities: In the paragraph of claim 54 bridging pages 2 and 3 of Applicant's response, Applicant should review their definition of the variables R^{19} , R^{20} , R^{12} , and R^{13} . Numerous possibilities for these variables have been omitted from claim 54, in comparison to the definitions of these variables in originally-filed claim 1. In particular, originally-filed claim 1, page 57, line 27, from the word "aralkyl" to line 30, up to the word "aryl", is not found recited in new claim 54. At claim 54, line 23, "heteroaralkenyl" is misspelled. At claim 54, page 3, line 5, "haloalkoxy" is misspelled. At claim 54, page 3, line 18, "carboxamido" is misspelled. At claim 54, page 3, line 19, "pseudohalo" is misspelled. At claim 54, page 3, line 21, "aralkenyl" is misspelled. At claim 54, page 3, line 23, "heterocyclalkenyl" is misspelled. At claim 54, page 3, line 24, "heteroaralkoxy" is misspelled. In the formula recited in claim 56, "HC" should be changed to "HCl". Also, claim 56 does not end with a period. At claim 58, line 2, "which" should be inserted after "moiety". At claim 60, line 3, a comma should be inserted after "RNA". At claim 70, line 1, a comma should be inserted after the definition of A. Appropriate correction is required.

5. The effective filing date of instant claims 54, 55, and 57-70 is deemed to be March 22, 2001, the filing date of the instant application. Instant claims 54, 55, and 57-70 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/191,186 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, does not disclose all of the R groups recited in formula I of instant claims 54 and 55.

The effective filing date of instant claim 56 is deemed to be March 22, 2000, the filing date of provisional application 60/191,186. Instant claim 56 is deemed to be entitled under 35

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U.S.C. 119(e) to the benefit of the filing date of provisional application 60/191,186 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 54, 55, 57, 59, 63, and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 93/14779. The WO Patent Application '779 teaches a compound at page 22, Example 5, which anticipates Applicant's compound of formula I in which B is a carboxyl group; R is a cycloalkylene group combined with a $C(R^{10})_2$ group where R^{10} is hydrogen; A is $-NH(C=O)-$; and X is trifluoroacetate. In Example 6, the compound of Example 5 of the WO Patent Application '779 is reacted with an arginine derivative, which is a synthetic biological molecule, and the product is then conjugated to the amino group of a solid phase resin (which corresponds to Applicant's surface) in Example 7.

8. Claims 54, 55, 57, 59, 63, and 70 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 93/14779 as applied against claims 54, 55, 57, 59, 63, and 70 above, and further in view of Abrams et al (U.S. Patent No. 5,679,778) or Ashkenazi et al (U.S. Patent No. 5,329,028). Compound 5 of the WO Patent Application '779 differs from Applicants' elected species in that compound 5 comprises a trifluoroacetate salt rather than a hydrochloride salt. Abrams et al teach bifunctional linkers in which if a hydrazine group is present, it is present in acid addition salt form. Hydrochloride salts are exemplified. See, e.g., column 2, lines 25-33; column 4, lines 23-24; column 5, lines 22-25; and column 7, lines 34-35. Ashkenazi et al teach bifunctional linkers in which if both hydrazide and maleimide functional groups are present, the

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hydrazide group is present in the form of a hydrochloride in order to prevent reaction between the two groups (see, e.g., column 6, lines 11-17, and column 9, lines 3-6). It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form compound 5 of the WO Patent Application '779 as a hydrochloride salt rather than as a trifluoroacetate salt because both Abrams et al and Ashkenazi et al disclose hydrochloride salts to be useful salt forms for hydrazide-containing linkers, because the particular salt would not have been expected to affect the reactivity of the hydrazide group of compound 5 with the aldehyde group present in the tBoc-N⁸-nitro arginal reactant, and because the substitution of one known functional equivalent for another is prima facie obvious.

9. Claims 59-69 are rejected under 35 U.S.C. 103(a) as being obvious over Berninger et al (U.S. Patent No. 5,856,571). Berninger et al '571 teaches using hydrazide-containing linkers having the structures at column 5, lines 22-26, to crosslink components A and B (see column 4, lines 47-56). The linker can be reacted first with component A and then with component B, or first with component B and then with component A (see, e.g., column 3, line 64 - column 4, line 9, and column 5, lines 37-41). Component A comprises a group which is reactive with the functional group X of the linkers, and X can be a carboxylic acid group or a reactive carboxylic acid group (see, e.g., column 5, lines 44-49; column 6, line 59 - column 7, line 7; column 9, lines 13-16). Component A can be a solid support, or a protein, or biotin derivatized to present an amine group for coupling (see column 9, lines 21-58; column 11, lines 5-8 and 17-36; and column 12, lines 21-24). Component B comprises a carbonyl moiety, such as an aldehyde or ketone moiety, which the hydrazide group of the linker reacts with and forms a stable semicarbazone linkage (see column 5, lines 10-19, and column 9, lines 17-20). Component B

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can be an antibody, DNA, RNA, or a solid support (see column 12, lines 50 - column 13, line 22). Berninger et al '571 does not exemplify a linker having a functional group X which is an amine reactive group. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form a hydrazide-containing linker according to Berninger et al '571 in which the functional group X is an amine reactive group because Berninger et al teach that X can be an amine reactive group such as a carboxylic acid group or a reactive carboxylic acid group and because Berninger et al teach that such a linker structure would have the benefit of not requiring the use of temporary blocking groups (see column 5, lines 43-49), and because such a linker structure would permit the crosslinking of a component A which comprises available amino moieties, such as proteins (see column 11, line 57 - column 12, line 3). While Berninger et al '571 does not teach its hydrazide-containing linker in salt form as is specified in instant claim 54 (i.e. does not teach Applicant's HX group), reactant and/or process limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to instant claims 68 and 69, the order of reaction specified in method claims 62 and 64 does not impart patentability to product-by-process claims 68 and 69, respectively, because the same product results regardless of whether the linker of Berninger et al is first reacted with component A or component B.

10. Claims 54, 57-61, 64, and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by the Scott et al article (Bioorg. Med. Chem. Lett., Vol. 6, pages 1491-1496). The Scott et al article teaches a compound of formula 2 (see, e.g., the Abstract) which anticipates Applicant's compound of formula I in which B is a succinimidyl ester; R is a combination of a C(L), a N(R¹⁰), and two C(R¹⁰)² groups; A is -NHNH(C=O)-; and X is trifluoroacetate. The compounds

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are used first to react with the amine group of a lysine residue in a protein, e.g., a monoclonal antibody, so as to introduce a hydrazide functionality into the protein, and then to react with a carbonyl group of a drug such a doxorubicin (see, e.g., the abstract and Schemes 5 and 6).

11. Claims 54, 57-61, 64, and 69 are rejected under 35 U.S.C. 103(a) as being obvious over the Scott et al article (Bioorg. Med. Chem. Lett., Vol. 6, pages 1491-1496) as applied against claims 54, 57-61, 64, and 69 above, and further in view of Abrams et al (U.S. Patent No.

5,679,778) or Ashkenazi et al (U.S. Patent No. 5,329,028). The compound of the Scott et al article is a trifluoroacetate salt rather than a hydrochloride salt. Abrams et al teach bifunctional linkers in which if a hydrazine group is present, it is present in acid addition salt form.

Hydrochloride salts are exemplified. See, e.g., column 2, lines 25-33; column 4, lines 23-24; column 5, lines 22-25; and column 7, lines 34-35. Ashkenazi et al teach bifunctional linkers in which if both hydrazide and maleimide functional groups are present, the hydrazide group is present in the form of a hydrochloride in order to prevent reaction between the two groups (see, e.g., column 6, lines 11-17, and column 9, lines 3-6). It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form the compound of the Scott et al article as a hydrochloride salt rather than as a trifluoroacetate salt because both Abrams et al and Ashkenazi et al disclose hydrochloride salts to be useful salt forms for hydrazide-containing linkers, because the particular salt would not have been expected to affect the reactivity of the hydrazide group with the aldehyde group present in doxorubicin, and because the substitution of one known functional equivalent for another is prima facie obvious.

12. Applicant's arguments filed April 30, 2003 have been fully considered but they are not persuasive.

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The anticipation and obviousness rejections based WO Patent Application 93/14779 are maintained. The carboxy group present in the compound of Example 5 of the reference is an amino reactive moiety. A carboxy group reacts with an amino group to form an amide. While Applicant may not exemplify a carboxy group as being an amino reactive moiety, the patent law permits a genus to be anticipated by species other than those exemplified by the Applicant. Further, Applicant explicitly states at page 18, lines 30-31, of the specification that his amino reactive groups are not limited to the ones exemplified in the specification.

The newly presented claims, which no longer embrace derivatives, which require B to be an amino reactive moiety rather than a thiol reactive moiety, and which no longer permit A to be a direct bond to R, overcome the rejections based upon Schwartz et al '370, Sytkowski '758, Sivam et al '290, Whelihan '860, the Heindel et al article, and the Zara et al article set forth in the previous Office action.

12. Claim 56 would be allowable if rewritten to overcome the claim objection set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. In particular, Applicants' new claims, which do not embrace derivatives of formula I and which more narrowly define the variables A and B, required a new structure search in which the Scott et al article was identified and applied above. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

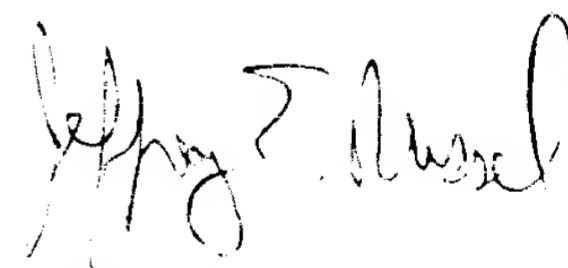
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel
June 9, 2003